Remarks

Claims 34-47 have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of all canceled claims in one or more continuation or divisional applications. Upon entry of the present amendments, claims 24-33 and 48-57 will be pending.

I. Notes and Objections

A. Priority

The Examiner has stated that, "[t]he first full disclosure of the elected sequence (SEQ ID NO:145) appears to be in PCT US98/23435 as SEQ ID NO:141. The instant claims are accorded the effective filing date of 11/4/98." *See* Paper No. 0604, page 2, second paragraph. Applicants respectfully disagree and traverse.

As stated in the present specification as filed, page 1, paragraph 1, International Application No. PCT/US98/23435, filed November 4, 1998, claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Nos. 60/064,911, filed November 7, 1997, and U.S. Provisional Application No. 60/064,911 discloses the presently elected sequence as SEQ ID NO:15. Therefore, the instant claims should be accorded a priority date of November 7, 1997.

Applicants respectfully request that the Examiner acknowledge the correct priority date is November 7, 1997.

B. Information Disclosure Statement:

The Examiner has stated that, "The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(l) states, 'the list may not be incorporated into the specification but must be submitted in a separate paper.' Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered." *See* page 2, lines 8-11 of Paper No. 0604.

Applicants respectfully request that the Examiner identify which particular references in the specification are not properly disclosed.

C. Specification

The Examiner has objected to the embedded hyperlinks in the specification. *See*

page 2, lines 22-24 of Paper No. 0604. Applicants have amended the specification to remove the computer executable code. Thus, Applicants respectfully request that this objection be reconsidered and withdrawn.

II. Rejections under 35 U.S.C. § 101/112:

Claims 24-57 have been rejected under 35 U.S.C. § 101 because, allegedly, "...the claimed invention lacks patentable utility due to its not being supported by a specific, substantial, and credible utility or a well established utility." *See*, Paper No. 0604, page 3, lines 9-11.

More particularly, the Examiner alleges the following:

> At no point is the specifically elected sequence tested for any of the listed associations, activities or expression patterns. At no point is a diagnostic test for any disease developed such that the elected sequence is shown to be linked diagnostically to a particular disease.

Page 3, lines 25-28 of Paper No. 0604. Applicants respectfully disagree. As a preliminary matter, Applicants note that claims 34-47 have been canceled without prejudice or disclaimer, therefore the rejection with respect to these claims is moot. With respect to claims 24-33 and 48-57, Applicants submit that a diagnostic test for disease based on the elected polypeptides does not have to be developed in order to disclose a specific, substantial and credible utility for the claimed polypeptide.

Moreover, Applicants point out that utility can exist for the claimed polypeptides "despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition." M.P.E.P. § 2107.01 (III) at 2100-35. "Usefulness in patent law . . . necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re* Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (Emphasis added).

The Examiner further alleges that the specification puts forth a "...laundry list of potential activities," which are "...general in nature...conflicting, [and] have widely varying causes or effects such that...one of skill in the art would not be readily able to determine a specific substantial and credible utility for the claimed polypeptides." *See* page 4, lines 12-15, Paper No. 0604. Applicants respectfully disagree.

First, Applicants submit that the disclosure of several uses for the claimed invention does not negate the specificity of any one of those uses. Indeed, the M.P.E.P. at § 2107.02 states "[i]t is common and sensible for an applicant to identify several specific utilities for an invention . . .". Further, "[i]f applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established." *Id. See also,* In re Malachowski, 189 U.S.P.Q. 432 (C.C.P.A. 1976); Hoffman v. Klaus, 9 U.S.P.Q.2d 1657 (Bd. Pat. App. & Inter. 1988).

Moreover, Applicants point out that according to the M.P.E.P. at § 2107.01, where Applicants disclose a biological activity, and reasonably correlate that activity to a disease or condition, Applicants have sufficiently identified a specific utility for the invention. *See* (at 2100-32, paraphrased, emphasis added). Stated in other words, so long as the correlation between the biological activity and the asserted use in a particular disease or condition is sufficient to convince one of skill in the art, then the specificity requirement of 35 U.S.C. § 101 is satisfied.

The present specification puts forth several specific utilities for the claimed polypeptides. These utilities are interrelated and rooted in the specific properties of the claimed polypeptide. For example, the HFVAB79 polypeptide has an amino acid sequence that is characteristic of a secreted molecule (comprising an N-terminal signal sequence which is cleavable by a type I signal peptidase), and is expressed primarily in the liver to a lesser extent in the testis (*See* specification Table 2, page 291, row 8: H0151, H0574, and H0038 corresponding to early stage human liver; hepatocellular tumor, re-excision; and early stage testes libraries, respectively, as defined in the specification in Table 4). Furthermore, in agreement with the properties of the HFVAB79 polypeptide, the specification states:

> The tissue distribution in liver tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of liver disorders, particularly those affecting the immune and hematopoietic systems, including hepatomas. Representative uses are described in the "Hyperproliferative Disorders," "Infectious Disease," and "Binding Activity" sections below, in Example 11, and 27, and elsewhere herein. Briefly, polynucleotides and/or polypeptides corresponding to this gene can be used for the detection, treatment, and/or prevention of hepatoblastoma, jaundice, hepatitis, or liver metabolic diseases and conditions that are attributable to the differentiation of

hepatocyte progenitor cells.

Specification page 29, paragraph 78, first 3 sentences.

This is not a general list of "potential uses for any protein involved in cell growth and differentiation," as alleged on page 4, lines 1 and 2 of Paper No. 0604. Rather, this is a specific statement that expression data indicates the claimed polypeptide would be useful for the detection, treatment, and/or prevention of related disorders, i.e., hepatoblastoma, jaundice, and hepatitis. (*See* Exhibit A, Kumar et. al., Basic Pathology, 6th edition, page 548, left column; page 518, right column to page 521, left column; and page 524, right column to page 533, right column). Indeed, post filing date art has demonstrated that a polynucleotide sequence encoding a polypeptide referred to as hGXIIB $sPLA_2$ and PLA2G13 (which is 99% identical to the claimed polypeptide) is differentially expressed in normal versus liver tumor tissues. *See* Exhibit B, Rouault et al., page 11501, left column, last two full sentences and Figure 7; and Exhibit C, Smith et al., page 863, left column, lines 9-13. Therefore, as stated in Applicants specification, polypeptides corresponding to this gene can be used to generate or select antibodies that specifically bind the HFVAB79 polypeptide, which provides a method for detecting a change in HFVAB79 expression, for example to diagnose a liver disorder, such as a hepatoma, by sampling bodily fluids or *in situ*. Thus, the present specification discloses a specific, substantial, and credible utility for the claimed polypeptides, which has been subsequently confirmed in the art.

The Examiner has also expressed a concern that a computational method was used to predict the cleavage point of the claimed polypeptides signal sequence and that this "has not been validated by producing the polypeptide *in vitro* and observing cleavage of and secretion of the actual sequence." *See* page 4, lines 21-22 of Paper No. 0604. Applicants respectfully submit that persons of ordinary skill in the art routinely utilize computational methods similar to that described on specification page 309, paragraph 750, to determine if a novel polypeptide contains a signal sequence, and if that signal sequence is cleaved. Indeed, in Exhibit B, Rouault et al., utilize the computation method described by Nielsen et al., Protein Engineering 10:1-6 (1997), a derivative of which was utilized in the present specification, to predict the signal peptide of a polypeptide which discloses a characterization of a polypeptide 99% identical to the claimed polypeptide. *See* page 11498, left column, 3rd full paragraph. Thus, even assuming, *arguendo*, that the signal peptide cleavage site of the claimed polypeptide were to differ from that disclosed in the

present specification, Applicants submit that the claimed polypeptide would still be secreted and would still possess a specific, substantial and credible utility.

The Examiner also states that sequence similarity alone does not support the assertion that a novel polypeptide has the same biological activity as its nearest homolog. *See* paragraph bridging pages 4-5 of Paper No. 0604. Applicants respectfully submit that this basis of rejection is not relevant to the present claims since the biological activity of the claimed polypeptide was not established by homology. *See* specification, pages 28-30, paragraph numbers 75-79.

Lastly, the Examiner has expressed a concern that "...for the asserted utility of prevention, diagnosis or treatment of a disease, one would need to know what disease is linked to the polypeptide, and in what way- i.e. does the disease result from too much or too little of the claimed polypeptide...[t]he need for such further research and experimentation clearly indicates that the asserted utilities for the polypeptides are not disclosed and therefore are not specific, substantial and credible utilities" *See* page 5, lines 16-24 of Paper 0604.

Applicants respectfully disagree. The present specification discloses that a change in the expression of the claimed secreted polypeptide is linked to hepatic disorders, such as hepatoma, and therefore the claimed polypeptide is useful, for example, in the diagnosis of hepatoma. Whether a liver disorder, such as hepatoma, is associated with too much or too little of the claimed polypeptide is not related to the question of utility. Nonetheless, Applicants submit that the specification clearly discloses several well-known assays that can be used to detect altered (*i.e.,* either increased or decreased) expression of the claimed polypeptide, such as radioimmunoassays, Western blot analysis and ELISA assays. *See* e.g., specification page 29, paragraph 77 and page 347, paragraph 854.

Based on the disclosure in the specification and the knowledge in the art at the time of filing, one of skill in the art would readily be able to detect either an increase or decrease of HFVAB79 polypeptide in patients suspected of having a hepatic disorder, such as a hepatoma. Therefore, the claimed compositions and methods are useful under §101 as asserted in the specification. Accordingly, Applicants respectfully request that rejection of claims 24-33 and 48-57 under 35 U.S.C. § 101 be reconsidered and withdrawn.

Claims 25-57 have also been rejected under 35 U.S.C. § 112, first paragraph because the claimed invention is allegedly "...not...supported by a specific, substantial, and credible utility...or a well-established utility...one skilled in the art clearly would not

know how to use the claimed invention." *See* page 6, lines 10-13, Paper No. 0604.

Applicants respectfully disagree. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. §101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-36. As explained above, claims 24-33 and 48-57 comply with the utility requirement of 35 U.S.C. § 101. Additionally, claims 34-47 have been canceled without prejudice or disclaimer; therefore, the rejection with respect to claims 34-47 is moot. Accordingly, Applicants respectfully request that rejection of claims 24-33 and 48-57 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

III. Rejections under 35 U.S.C. § 112:

The Examiner has rejected claims 34-47 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *See* page 7, lines 21-24, Paper No. 0604. Applicants respectfully disagree. However, claims 34-47 have been canceled herein without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of claims 34-47 in one or more continuation applications. Therefore, the rejection with respect to claims 34-47 has been rendered moot.

The Examiner also rejected claims 29-33, 41-47, and 53-57 under 35 U.S.C. § 112, first paragraph, because "[i]f a deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808." *See* page 7, line 18 and page 8, lines 1-7.

Applicants respectfully point out that the specification, as set forth in 37 C.F.R. § 1.809 (d), clearly describes at page 4, paragraph 13 and page 276, Table 1, row 8 that the HFVAB79 cDNA contained in ATCC Deposit No. 209368 was deposited at the ATCC on October 16, 1997. The specification clearly discloses that ATCC Deposit No. 209368 has been deposited under the terms of the Budapest Treaty on the International Recognition of

the Deposit of Microorganisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110-2209, U.S.A. (*See* page 4, paragraph 13). The Applicants respectfully submit that the specification is in compliance with 37 C.F.R. §§ 1.801-1.809.

Nevertheless, Applicants submit herewith the requested declaration regarding availability of the deposit made in connection with the present application under the Budapest Treaty.

Statement Regarding ATCC Deposit

> Applicants' agent hereby states that Human Genome Sciences, Inc., the assignee of the present application, deposited the HFVAB79 cDNA under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209 (present address). The deposit was made on October 16, 1997, accepted by the ATCC, and given ATCC Accession Number 209368. In accordance with M.P.E.P. § 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Number 209368 will be irrevocably removed upon the grant of a patent based on the currently pending claims, except as permitted under 37 C.F.R. § 1.808(b).

In view of the above, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been obviated. Accordingly, Applicants respectfully request that this rejection of claims 29-33, 41-47, and 53-57 be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the above-made remarks be entered and made of record in the file history of the instant application. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the examination of this application. Alternatively, if the Examiner believes that an interview would help resolve any remaining issues, Applicants urge the Examiner to call the undersigned to arrange an interview at their earliest convenience. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 that is not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: 9/28/04

Respectfully submitted,

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